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DEPARTMENT OF THE ARMY
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Listeriosis in man.

by J. Potel

Discourse No. 7, Listeriosis, a symposium at Giessen, Germany, 27 - 28 June 1957, pp 70-78. Supplement 1 to Zentralblatt fur Veterinarmedizin, 1958.

I should like to base my report on a comprehensive survey of more than 8 years of my own work in this field, in addition to the most important papers of other authors, in which connection I shall try to keep speculation to a minimum.

As is well known, European research in the field of adult listeriosis, following Nyfeldt's initial work, has received new impetus in 1951, when Seeliger et al. for the first time observed listeriosis in an adult, after Seeliger had established the identity of "*Corynebacterium infantisepticum*," which we had found in 1949 in newborn at Halle, with *List. monocytogenes* on the basis of comparative tests with subcultures of such strains made available to us.

In retrospect one can only wonder how it was possible that this relative frequent human illness had escaped detection here for such a long time and still is unknown in many locations. Fortunately Germany occupies a special place in this respect, as research centers have been established in both parts of our country, which attempt to cover their areas as closely as possible, enabling us to prepare a map on the occurrence of human listeriosis in Germany (Potel and Seeliger). Of course the map is outdated by now, since findings of listeriosis are steadily increasing.

In this report I shall use only, bacteriologically established cases of listeriosis and those personally examined or checked by me, which in addition to 58 strains from animals include 247 human cases, including 85 isolated by me up to 20 April 1957. I feel justified in making certain pronouncements on the basis of this figure which I believe to be the largest number treated at one research center, especially so in view of our attempt to cover the clinical and epidemiological aspects of our cases, on which several papers have already been published (summarized presentation by Potel).

All strains isolated from these cases of human listeriosis revealed the characteristics of *List. monocytogenes*. () Certain differences were noted solely in the fermentation of carbohydrates of some sugars, and in differentiation as to serologic type or in quantitative antigen synthesis within the same serotype. Serotype 1 was by far most frequently represented (226), a large interval apart from serotype 4 (18). Serotype 3 was found in humans only twice, serotype 2 only once. I should like to add here that I had the opportunity recently to test a "*diphtheria bacterium strain*" from the collection of an institute, which also was proved to belong to serotype 2 of *List. monocytogenes*.

As a rule no difficulties were encountered in pathogen determination, although this is stressed at times by others. In regard to older test material delayed by transportation (autopsic material with corresponding secondary im-

purities), tellurite broth has served us well. Isolation from such material certainly could be improved through utilization of several methods, e.g. the cold culture after Gray, tellurite and sodium chloride-containing media. There is no difference here from usual bacteriological procedure. In examinations of gynecological material following delivery of listeria-infected children Patocka and Kencikova in Prague have had success with the cold culture after Gray.

There are as yet no pronounced selective enriched nutrients for listeria, other than guanofuracin, with which we have not had any experience in our area.

Considering my past experiences I tend to think that better knowledge of listeria depends less on the improvement of test methods and more on the know-how and "remembering" on the part of the practising physician. Furthermore it is my opinion that the law requiring the reporting of listeric disease and death cases, which has been in force in Central Germany for two years already due to our initiative, will heighten the interest. In order to attain better knowledge of listeria and its frequency, post mortems should be accomplished regularly on all questionable cases, especially on bodies of children. When it was decreed in Magdeburg that all still-births be subjected to section, the number of cases of newborn listeriosis immediately rose. A similar situation exists elsewhere in large hospitals with close interdepartmental cooperation.

Clinical forms of human listeriosis known to date.

As in the animal, so in man the clinical forms are various. The mode of infection as well as constitutional and dispositional factors, discussed further on, certainly are decisive for the diverse progressions. In this respect listeriosis is no different from other infectious diseases. I am of the opinion that human listeriosis is not limited to the clinical forms to be discussed below.

The sequence of presentation of the individual clinical aspects of human listeriosis is ordered according to their frequency to date.

Listeriosis of pregnant women and newborn.

According to available reports this is the most frequent and most important of the human types of listeriosis. Murray, too, expresses this view after acquainting himself with our papers. Among the cases examined or checked by me there were 185 (75%) cases of pregnancy and newborn listeriosis. When I mention these two terms in association this is justified because both diseases belong together. The general listeric infection of the pregnant woman is the preliminary condition for the diaplacentally effected infection of the fetus, in which the disease as a rule can be recognized only after delivery or abortus.

The earliest point in pregnancy at which general infection of the woman may set in has not yet been established. During the past few months we have examined, both bacteriologically and serologically, women with miscarriages in whom induced abortion was improbable. In about 100 patients examined so far (examinations are continuing) listeria were excluded as causative agents. For the present I believe that a fully developed placental circulation (that would

be about the 4th month) is a preliminary condition for the possibility of genesis of a listeric infection. As we have already reported, our "youngest" pregnancy terminated by expulsion of a dead child with listeriosis (granulomatosis infantiseptica) was at the end of the 5th month of gestation. Moreover, we were able to isolate the pathogen from the flowing blood of the woman. The general listeric infection of the pregnant woman seems to progress more or less inapparently, as a passenger, since the symptomatology is quite meagre, if any: Suddenly appearing fever, chills, sometimes "inflammation of the renal pelvis," at times diarrhea or dyspnea. Here, too, it is astounding how much a precise anamnesis and inquiry can contribute. We have seen pronounced symptoms, yet the majority reveals only fever a few hours prior to parturition, which may be interpreted as a reaction of the parental organism to the uterine focus of infection represented by the infected placenta and the child.

Judging from observations made to date the pregnant and postparturient woman is able to cope with the infection and the disease (all patients recovered), contrary to other forms of listeriosis which show a very high rate of mortality, and also contrary to the diseased animal, or better, the laboratory animal, which after abortion or birth succumbs to severe purulent metritis.

Our own observations to date of late pregnancies after delivery of a listeria-infected child even allow the conclusion that danger of relapse (endogenously) does not seem to exist. We were able so far to follow up on 35 such pregnancies and to run constant bacteriologic and serologic tests. Thirty-two times a healthy child was born, 3 times a premature or still birth without clinical signs of listeriosis and with negative results of bacteriologic and serologic tests.

In this connection the problem of frequency of abortion and listeriosis must again be discussed briefly. We (Potel and Alex) had already reported in one paper that no statistically demonstrable frequency of miscarriages could be found in the anamnesis of our patients. I do not think our earlier reports could be interpreted any other way. Nor do I think that serologic tests alone can solve this problem. We must rest on the foundation of facts available to us through bacteriologic examinations. Exclusive serologic tests leave too much room for speculation, at least at the present stage of our knowledge regarding listeriosis-serology.

Much more serious is the course of fetal listeriosis, the terminus of the infective chain of this form of listeriosis. As a rule it is fatal when untreated, providing only bacteriologically tested and determined cases are considered. These statistics can be improved upon only by early recognition and treatment of the infection. They cannot become favorable if listeriosis is diagnosed in the child, when previous infection of the mother had been ignored or not recognized. The majority of fetuses die in the mother (the movements cease), another large portion are born moribund. Birth usually takes place before the term due to the infection.

Pathologic-anatomical findings then expose the septic events. The designation "granulomatosis infantiseptica" characterizes them well. But even clinically one can find signs of disease in the pulmonary area of viviparous, listeria infected children, either by auscultation or roentgenologically, giving the

impression of pneumonia due to inspiration of liquor amni (which it is). Children with such a condition are frankly dyspneic, bluish, and show convulsive manifestations. The pathogen may be isolated from all organs which show macroscopically (sometimes only histologically) recognizable changes, even from swabs of the middle ear (often otitis media is involved), the bile, gastric fluid and in the meconium.

An attempt should be made to determine the pathogen as early as possible. In cases of existing infection, bacterioscopic findings were obtained in every one of our cases from the meconium. This should be remembered in connection with suspicious anamneses or clinical suspicions, which is the reason why we have for many years demanded a routine examination of the meconium in all premature births and questionable cases. Even clinicians (Erdmann, Brenning and others) have concurred in this demand which is easily met in a clinic. The increase in cured listeriosis among newborn, diagnosed by way of this test method and then treated, is proof of the correctness of our demand. While of 130 cases of newborn listeriosis in the years 1949-1955 only 11 (4%) were kept alive, cures amounted to 7 out of 50 cases in 1956 (14%). Judging from the answers to our inquiries (Potel, Martinek) the children are doing well.

Excluded from these figures are those cases which did not succumb to acute listeriosis, but died of later complications such as intoxication or hepatitis. It should not be concealed that the possibility of a chronic hepatic injury remains after overcome newborn listeriosis, as we have observed, since the liver has been found to be enlarged upon clinical examination. On the other hand, animal experiments have shown that restitutio ad integrum (histologically) takes place after recovery from listeriosis.

Listeriosis of the central nervous system.

Listeriosis of the central nervous system is the next most frequent form of human listeriosis. Its clinical signs are no different from those found in meningitides and encephalitides of other etiology. The purulent cerebrospinal fluid sometimes contains increased monocytic elements (Flamm et al.). We have not been able to make this observation in our own cases, however. The decrease in sugar pointed out by Seeliger et al. in their own isolated findings, has also been remarkable in our cases, a circumstance of possible differential-diagnostic value. Upon poor prognosis of this form of listeriosis the patient's fate depends largely on therapy, following bacteriologic diagnosis and sensitivity tests. Still, a large percentage of patients may then be cured.

The course of the disease seems to depend on the localization within the central nervous system. Listeric encephalitis is less favorable prognostically, as shown in the cases reported by Eck. His observations are conspicuous not only by their periodic frequency but also by the fact that in 7 out of 9 bacteriologically determined cases serotype 4 was found (6 times 4a, once 4b, Seeliger). The frequency of listeriosis of the central nervous system in the area of Leipzig in the year 1956 cannot be explained off-hand.

It also seems remarkable to me that in some examination points of my area of observation only listeriosis of the central nervous system was diagnosed, for which I cannot give an account either. Infantile listeriosis of the central

nervous system may, just as tuberculous meningitis, cause hydrocephalus, as we have observed in two of our cases. This circumstance should not deter treatment in every case, however. Of 27 cases of listeriosis of the central nervous system in our area of observation in 1956, 7 were cured. I should like to make one more remark in this connection. A differentiation not only according to the place of localization but also according to progression should be justified, namely the "primary" listeriosis of the central nervous system (as basic disease and cause of death), as found in children and agricultural persons, and the "secondary," which is grafted on top of another basic disease (carcinoma, tuberculosis) and then becomes the cause of death.

Adenoid forms of listeriosis.

In this form of listeriosis a simultaneous increase in monocytic elements in the peripheral blood is often found, which as a rule is lacking in the forms discussed heretofore.

This characteristic of angina with increase in monocytes had been reported by Nyfeldt in 1929 in the description of case of human listeriosis. Clinically, listeriosis in the lymph glandular area (a possible explanation for monocyte increase) of the pharynx and throat develops as angina, diphtheroid, lymphadenitis.

Discussion persists on whether listeria are the pathogens of infectious mononucleosis, as initially believed by Nyfeldt. Krepler and Flamm afford this problem a great deal of space in their latest summary. If the papers of the last few years are interpreted, however, especially those of Girard and Murray, then it seems that the adenoid form of listeriosis and infectious mononucleosis are two independent diseases having a few symptoms (such as monocytosis) in common.

It is hoped that expanded research in the following years will result in even greater clarity concerning this form of listeriosis, about which there are relatively few papers so far based on thorough bacteriologic tests. Sole serologic tests will not advance our cause.

Since various lymph glandular areas of the throat and pharynx may be attacked by listeria, the clinical symptoms are correspondingly different. The German-language literature shows only the report by Urbach and Schabinski on an epidemic of Pfeiffer's glandular fever with verification of listeria among student nurses and in cases of questionable diphtheria. So far we have not been able to isolate listeria from pharyngeal swabs. On the other hand, I recently had the opportunity at another station to test a questionable germ isolated from a pharyngeal smear, which then turned out to be *Listeria monocytogenes*, serotype 4a.

Perhaps the adenoid form of listeriosis should include the oculoglandular form observed in recent years only in Russia by several authors and in one case in Czechoslovakia. The Russian reports are in part supported only by serologic tests. The paper of Moroskin and Lebedewa shall be discussed later.

Sepsis listeriosa (without listeriosis of newborn).

This form is especially difficult to differentiate from the just discussed adenoid form, since transitions may be quite rapid, as on the whole a sharp delineation of the individual clinical progressions is not always possible in human listeriosis.

The disease progresses with septic temperatures, "typhous" without visible organix manifestations, often as a complication of another basic illness. Diagnosis without bacteriologic tests is impossible. And these may fail intra vitam in this form of listeriosis (Seeliger et al.). In Germany, as in other countries, only isolated reports on septic forms have appeared, due not less to the difficulties of diagnostic of this form of listeriosis, in which the blood culture method still moves along well-worn paths. In our area there were only 3 bacteriologically assured cases. At this point it is relevant to discuss the examinations of Moroskin and Lebedewa. They report in their detailed account, unfortunately without considering the newer literature, on their experiences and isolation of 73 cases of human listeriosis and 4 cases of rodents. The majority of isolations were accomplished by means of blood culture by utilizing different nutrient media. The cultures were incubated for 3-12 days with interpolation of several passages.

Conspicuous in comparison to strains examined elsewhere, are: The rapid death of the cultures, the morphologic similarity to Diphtheria bacteria, partly missing motility, the different reaction in the biochemical series, the low pathogeny. Ability of the isolated strains to agglutinate with listeric whole sera does not constitute absolute proof of identity with *List. monocytogenes*, according to our present knowledge of antigen association with other pathogens. Unfortunately it was impossible to obtain strains from Moroskin. A journey to Kiew planned for this month had to be cancelled due to my departure from Halle. During the course of an exchange of correspondence Moroskin informed me of his decision to group his strains with *List. monocytogenes* after all, in spite of the deviations just mentioned. He believes them to be identical with the characteristic of Hülphers' pathogen and the bacteria described by Murray, as reported by Seeliger in the first edition of his book, *Listeriosis*, page 117. However, compared to the strains we sent to Moroskin, considerable deviations were apparent.

A few words more on the aspects of the disease as observed by Moroskin and Lebedewa. In 72% of 124 patients, i.e. 88 (this figure differs from the figure of 73 given by letter) the pathogen could be isolated from the blood, with or without serologic demonstration of antibody, while the diagnosis for the remaining patients was accomplished by serologic means only. 65% of these patients showed the visceral (typhous, septic), 15% the glandular, 5% the neural, 1% the oculoglandular, and 14% the combination form. The high percentage of septic listeriosis is apparent, among which listeriosis of newborn (they were not seen at all) was not included, as Moroskin informed me.

If listeriosis was indeed involved in this material, the deviation in the distribution of frequency of the various disease forms would be of interest. Perhaps this pathogen is a *Corynebacterium* not belonging to *List. monocytogenes*, a circumstance tending to increase our knowledge of atypical *Corynebacteria*.

We have seen *Corynebacteria* in the course of typing *listeria*-suspected strains from abroad which upon test agglutination reacted serologically with *listeria* O sera, but did not belong to *List. monocytogenes*.

I have given so much space to Moroskin's work, since, aside from the earnestness of the undertaken tests, a great amount of material is involved which cannot be checked elsewhere under existing conditions and thus cannot be subjected to clarification.

Diagnosis.

It should not be necessary to report on the details of bacteriologic diagnosis of listeriosis, since the preceding affords a selection of material to be examined. As a theorist I cannot contribute further to the clinical diagnosis. I should like to stress once more that we must suggest extreme caution, based on our experiences, in attempts to diagnose listeriosis by sole serologic methods; single tests are generally useless in any case and not worthy of discussion.

Therapy.

Concerning therapy, there should be unanimity by now in view of the multitudinous tests in vitro and in vivo, on the best suitability of a combination thrust therapy of sulfonamides and antibiotics, in connection with which the bacteriologist, who sees the dark side of "hospitalism" in his daily business, must again and again stress the control of antibacterial therapy. By the way, the strains isolated by Moroskin were less susceptible to penicillin (30 IE/ml) as *listeria* usually are. The limits imposed on therapy have been discussed already.

Epidemiology and prophylaxis.

It is conceivable that the hygienist cannot be satisfied with the improvement of test methods and of bacteriologic diagnosis, since he is bent upon recognition of the epidemiological connections, in order to present suitable means of prophylaxis.

If one looks at a larger summation of disease material it becomes apparent that the frequency of human illness does not stand in any relation to the possibilities of infection, which ought to be considered quite great in view of the dissemination of the pathogen among animals. Why does the pregnant woman fall ill more frequently than the nonpregnant? Why do we find listeriosis predominantly among children, older persons or in persons engaged in agriculture? The answer to the last part is easy to find. These persons are more often and more massively exposed to infection. The high percentage of pregnancy listeriosis may be ascribed in part to the fact that a genuine organotropy exists, as shown in experiments conducted by us and others, of *List. monocytogenes* to the pregnant uterus and placenta. It may even be suspected that a toxic effect of the pathogen is involved, since an abortion may be triggered in the pregnant animal a few hours after infection.

Youth and old age seem to be constitutionally more susceptible to attack by a listeric infection, just as starvation and a poor general condition (due

perhaps to a chronic disease) seem to predispose to listeriosis. Especially the last period of time has shown an increase in reports of human listeriosis observed as a complication of a basic disease. Recently a case seen by Hussels and Koehn in my present home town of Berlin concerned a woman who had suffered carcinoma as a basic illness and whose cause of death was listeric meningitis.

Therefore constitutional and dispositional factors are of great importance to the illness following listeria infection. This would mean that the pathogen's virulence is not great for man, and the index of contagion low. Accordingly, listeriosis would be grouped with the so-called fateful diseases.

Considering the preceding, I should like to go as far as to attempt a division of listeriosis, as suggested by Beer and Seffner for animal listeriosis, into primary (pregnancy listeriosis, listeriosis in children, and others) and secondary (listeriosis with another basic disease). This division would take into consideration the doubts about the absolute pathogeny of listeria, as recently advanced by Kroeger, without however sharing his opinion that listeria are to be accepted only as accompanying germs.

Regarding the seasonal frequency of human listeriosis, one would think that no dependency as to season exists. For this reason we thought it conspicuous that our own material of the years 1955, 1956 showed an "accumulation" of human listeriosis during the months of June-September. Foreign cases with seemingly similar circumstances have not been included, since the date on which the pathogen was isolated had not always been imparted.

Do chances of infection exist more often in summer? The answer to this question will be forthcoming as soon as we know the mode of infection in man. We had assumed oral infection in the case of pregnancy listeriosis and the parenteral path in the case of listeriosis of the central nervous system.

Even though veterinary science in our time is paying more attention to the epizootology of listeriosis, the past years nevertheless have brought no important advances in the recognition of the infectious chain animal-man. As shown by the joint work of Beer and Seffner, no direct connection between the occurrence of animal listeriosis and human illness can be perceived. A direct contact infection could not be demonstrated, so that all declarations concerning the path of infection are marked by a certain insecurity. To be sure, our assumption that transmission may be effected by way of insufficiently pasteurized milk has received support from further findings in cow's milk in other quarters.

On the other hand the value of serologic tests that we conducted on cattle, horses, sheep, swine and dogs has diminished due to our more recent experiences with serologic cross reactions, even though we tried to undermine them at the time by investigations as to clinical illness. Without a doubt we must expect numerous possibilities of transmission and infection in connection with the chance of listeric sheddings by the animal, without visible signs of disease, reserving a considerable role to dirt infection.

Our concept that human infection, aside from diaplacental transmission, ends blindly, should be subjected to revision, for in Czechoslovakia Patocka's research group has reported on human contact infections. A pregnant doctor

fell ill with listeric meningitis following treatment of newborn listeriosis; the anginal pharynx of a midwife who had assisted in the parturition of a woman with listeriosis yielded listeria; a healthy newborn is bedded next to a newborn with listeriosis and falls ill with listeric meningitis. The lastly mentioned case certainly is due to transmission by the nursing personnel. The listeric angina in the midwife seems significant to me, since no constitutional or dispositional factors seemed to be involved, as were present in the pregnant physician! It may become the starting point for further diseases. For this reason it was certainly good that we have several times made the suggestion to equate the parturition of a listeric woman with septic abortion and all its consequences.

And so, as a conclusion to our considerations, we arrive at prophylaxis. For the human being it is at present limited to general rules of conduct, such as cleanliness, especially in handling animals, avoidance of animals by pregnant women, consultation of a physician when an unexplained fever with decrease in the child's movements occurs during pregnancy. Unobjectionable pasteurization of milk must be guaranteed. Perhaps the deviations in this process in the Federal Republic and in Central Germany explain the numerous findings of pregnancy listeriosis in Central Germany and the isolated cases in the Federal Republic. The rules of food administration must be supplemented.

Not only is it necessary to inform physicians, midwives and welfare agencies of the new knowledge about listeriosis -- the mandatory report belongs to this category --, but also to illuminate the people in skilful ways through the responsible agencies, as is being attempted, for example, by the Hygiene Museum Dresden by means of a pamphlet designed by us.

It is hoped that the close and necessary cooperation between veterinarians and physicians will gradually close the gap in our knowledge of listeriosis, in order to reduce the importance it presently holds among human infectious diseases.